Translation

PATENT COOPERATION TREATY

PCT/JP2003/00405

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 104F1002	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/JP2003/004052	International filing date (*day/month/year*) 28 March 2003 (28.03.2003)	Priority date (*day/month/year*) 23 October 2002 (23.10.2002)
International Patent Classification (IPC) or national classification and IPC A61K 38/17, 9/19, 35/12, 47/36, A61L 27/22, 27/38, A61P 41/00		
Applicant INOUE, Kazutomo		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report
   ☐ Box No. II Priority
   ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   ☒ Box No. IV Lack of unity of invention
   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   ☐ Box No. VI Certain documents cited
   ☐ Box No. VII Certain defects in the international application
   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 15 March 2004 (15.03.2004)	Date of completion of this report 09 November 2004 (09.11.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2003/004052

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is language of a translation furnished for the purpose of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ The international application as originally filed/furnished

☐ the description:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____, as originally filed/furnished

pages* _____, as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/JP2003/004052

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5, 8-19

because:

☒ the said international application, or the said claims Nos. 5, 8-19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 5, 8-19.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ see Supplemental Box for further details.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Claims 5 and 8-19 pertain to methods for treatment of the human body by therapy, and thus relate to subject matter which does not require international preliminary examination by this International Preliminary Examining Authority, under the provisions of PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

INTERNATIONAL PRELI[redacted]ARY REPORT ON PATENTABILITY

I[redacted]ional application No.
PCT/JP2003/004052

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   See supplemental sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4, 6-7 .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

Claims 1-4 relate to angiogenesis inducers containing fibrin.

Claims 6-7 relates to particulate preparations obtained by freeze-drying fibrin.

Claims 1-4 and 6-7 have in common preparations containing fibrin; however, preparations containing fibrin are disclosed for example in document WO 00/38752 A and are, therefore, not novel. This common feature is thus not a special technical feature in the sense of the second sentence of PCT Rule 13.2.

Claims 1-4 and 6-7 thus do not satisfy the condition of unity of invention.

INTERNATIONAL PRE[illegible]NARY EXAMINATION REPORT

International application No.
P[illegible]JP 03/04052

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-4, 6-7	NO
Inventive step (IS)	Claims		YES
	Claims	1-4, 6-7	NO
Industrial applicability (IA)	Claims	1-4, 6-7	YES
	Claims		NO

2. Citations and explanations

Documents

Documents cited in the international search report

1. WO 00/62833 A (The Research Foundation of State University of New York), 26 October 2000
2. US 2002/150879 A (Eugene A. Woltering *et al.*), 17 October 2000
3. JP 2002-506344 A (Fidio Advanced Biopolymers SRL), 26 February 2002
4. WO 00/64376 A (C. R. Bard, Inc.), 2 November 2000
5. JP 2000-119194 A (Hiroko Yanaga), 25 April 2000

Documents cited for the first time here

6. C. Okubo *et al.*, "Seitai kenbikyou-teki ni kansatsushita soushou chiyu katei" Dai 21 Kai Sosho Chiyu Kenkyukai, 1992, vol. 12, no. 11, pp. 2907-2913
7. H. Okamoto *et al.*, "b-FGF wo kanwashita 'fibrin' nori 'sheet' ga hiben-nai kekkan-kei ni oyobosu eikyou", Dai 22 Kai Sosho Chiyu Kenkyukai, 1993, vol. 13, no. 11, pp. 2612-2614
8. JP 6-199685 A (E. R. Squibb & Sons, Inc.), 19 July 1994 & AT 244581 A & AU 676201 B2 & AU 4887893 A & BR 9304185 A & CA 2108104 A1 & CN 1091315 A & CZ 9302117 A3 & DE 69333080 D1 & DE 69333080 A & DK 592242 A &

EP 0592242 A1 & EP 1266666 A2 & ES 2065294 A1 & ES 2202306 A & FI 934440 A & HU 66587 A2 & IL 107211 A & MX 9306272 A1 NO 933624 A

9. JP 61-178927 A (Serapharm GmbH & Co. KG), 11 August 1986 & AT 13810 A & AT 20824 A & DE 3171072 D1 & DE 3175003 D1 & EP 68047 A2 & EP 68048 A2 & EP 68149 A2 & JP 58-038216 A & JP 58-38217 A & JP 58-36545 A & US 4427650 A & US 4427651 A & US 4442655 A

Explanations

a. The inventions set forth in claims 1-4 are not novel and do not involve an inventive step in the light of document 1.

Document 1 (see claims 12-16 and 19 and example II, III and V, etc.) discloses an angiogenesis device which includes cells, microcarrier particles (dextran or the like) and a fibrin matrix, and also mentions the addition of a growth factor to the aforementioned device.

b. The inventions set forth in claims 1 and 3-4 are not novel and do not involve an inventive step in the light of document 2.

Document 2 (see claims 14-18 and 23-24, etc,) discloses the fact that when tissue is embedded in a matrix comprising fibrin and cultured after adding a medium which includes a growth factor, angiogenesis is produced.

c. The inventions set forth in claims 1-3 are not novel and do not involve an inventive step in the light of document 3.

Document 3 (see claims 1, 19 and 23-25, etc.) discloses biological material which includes cells including endothelial cells, hyaluronic acid and collagen

(polymers degradable in the body), and fibrin, for use in surgery in order to enhance the biological process of angiogenesis of tissue.

d. The inventions set forth in claims 1-2 and 4 are not novel and do not involve an inventive step in the light of document 4.

Document 4 (see claims 21-22; page 8, lines 12-22; page 17, lines 2-3; page 17, lines 19-27; and page 19, lines 1-14) discloses a method for promoting revascularization, which comprises transplanting into the tissue a blood clot (fibrin) formed from blood outside the body; it also mentions the possibility of transplanting the blood clot (fibrin) and a growth factor into tissue together with a biodegradable material.

e. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of document 5.

Document 5 (see claims 1 and 2 and paragraphs [0014] and [0008], etc.) discloses an agent comprising fibrin for promoting production of TGF-α and/or TGF-β, and promotion of production of TGF-β in epithelial cells and fibroblast cells in a culture medium with added fibrin (fibrinogen preparation BeriplastP), and mentions that angiogenesis was seen and repair of tissue injury occurred rapidly after topical administration of TGF-β.

f. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of document 6.

Document 6 (page 300, right column) discloses the fact that when a tissue adhesive (Beriplast) was applied to a transparent window placed in the ear (rabbit ear

chamber; REC) in order to observe the microcirculation, the structure of the microvascular network inside the REC was good.

g. The invention set forth in claim 4 is novel and does not involve an inventive step in the light of newly cited document 7.

Document 7 (page 177, methods and results) states that in a group of rats in which a fibrin glue sheet was placed on the surface of an isolated skin flap made on the abdominal fascia, no marked change was noted in the vasculature within the skin flap; however, marked angiogenesis was noted in the group in which a sheet of fibrin glue mixed with b-FGF was similarly placed.

h. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of newly cited document 8.

Document 8 (see claims 1, 32, 59 and 60, and paragraphs [0113] and [0128], etc.) discloses a method of using a fibrin sealant wherein the desired site is brought into contact with a composition containing fibrin monomer, which is converted into fibrin polymer to form a fibrin sealant, discloses a method for producing a composition containing fibrin monomer from fibrinogen, characterized by solubilizing a non-crosslinked fibrin polymer obtained by bringing a fibrinogen-containing composition into contact with a thrombin-like enzyme, gives applications of aforementioned compositions such as suturing of tissues and organs, treatment of wounds and sealing of sites after surgery, indicates that when the desired site includes blood and a composition containing fibrin monomer is used, a fibrin sealant can be formed without employing another composition (diluent or alkaline buffer) because the fibrin monomer is converted into fibrin polymer by the

blood.

Given the aforementioned disclosures, document 8 can be considered to disclose particulate freeze-dried preparations which comtain fibrin monomer obtained by bringing fibrinogen into contact with a thrombin-like enzyme, and the fact that an aforementioned particulate freeze-dried preparation functions as an adhesive when brought into contact with a site of surgery or tissue which includes blood.

Document 8 does not disclose angiogenesis inducers; however, the description of the present application mentions application to wounds as an application of the angiogenesis inducers, and since it is evident from the description of the aforementioned applications that the compositions containing fibrin monomer disclosed in document 8 can also be used for application to wounds, the angiogenesis inducers claimed in claim 1 are indistinguishable from the invention disclosed in document 8 in this regard.

i. The inventions set forth in claims 6-7 are not novel and do not involve an inventive step in the light of newly cited document 8.

In addition to the items mentioned above in h., document 8 (see claims 59 and 60 and paragraphs [0107] and [0128], etc.) discloses solid compositions containing fibrin monomer, formed by freeze-drying an aqueous solution containing fibrin monomer; it also mentions that the freeze-dried fibrin monomer can be granular, and that when the desired site includes blood and a composition containing fibrin monomer is used, a source of supply of calcium ions is ideally added to the solution used in the solubilization step.

j. The invention set forth in claim 6 does not involve

an inventive step in the light of newly cited document 9.

Document 9 (see claims 1, 8-10 and 12, etc.) discloses a method for producing a freeze-dried preparation by freeze drying fibrin formed by the action of thrombin on fibrinogen, and cutting the freeze-dried preparation taken from the freezing die to give the moulded shape.

Document 9 does not disclose the shapes of the freeze-dried preparation; however, the shape of a preparation is merely a matter of design which can be decided at the discretion of a person skilled in the art; and a person skilled in the art could easily make the preparation particulate.

k. The invention set forth in claim 7 does not involve an inventive step in the light of document 9.

Addition of calcium when obtaining fibrin from fibrinogen and thrombin is known in this technical field.

l. The inventions set forth in claims 1-4 and 6-7 are industrially applicable.